Journal of Cardiovascular Pharmacology
20:858–863 © 1992 Raven Press, Ltd., New York

Arterial and Antihypertensive Effects of Nitrendipine: A Double-Blind Comparison Versus Placebo

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Summary: Arterial effects evaluated by carotid-femoral, brachial-radial, and femoral-tibial pulse wave velocity and antihypertensive effect evaluated by 24-h ambulatory blood pressure (BP) monitoring were measured in 17 hypertensive patients before and 24 h after once-daily nitrendipine (20 mg) administration. After a 15-day placebo period, a double-blind study of nitrendipine versus placebo was performed for 1 month. After nitrendipine dosing, BP measured by sphygmomanometer 24 h after the last drug intake showed a significant decrease as compared with the pretreatment period. Ambulatory BP mean values were also significantly decreased for systolic and diastolic BP (SBP, DBP). This decrease predominated during the day but was observed nocturnally only after 6 a.m. Twenty-four hours after the last tablet intake of nitrendipine, carotid-femoral and brachial-radial pulse wave velocities were significantly reduced, whereas femoral-tibial wave velocity was unchanged, indicating that markers of arterial rigidity might be substantially modified and that the modifications were partly unrelated to BP changes. The results provide evidence that in hypertensive subjects nitrendipine 20 mg given once daily for 1 month produces an arterial effect for 24 h, in association with BP reduction. **Key Words:** Hypertension—Arterial system—Ambulatory blood pressure—Calcium entry blockers.

Increasing evidence shows that 24-h ambulatory blood pressure (BP) measurements during normal activities better reflect the BP changes induced by an antihypertensive agent than do casual BP measurements (1,2). Specifically, when drug duration of action is analyzed, 24-h ambulatory BP monitoring has the advantage of showing the time course of the pharmacologic effect. There are also several well-known disadvantages of this method, however, mainly due to the limited possibility of repeated measurements, to sleep disturbances, and to the physiologic decrease in BP that occurs during the night. Thus, concomitant study of other hemodynamic markers complementary to BP measurements may be suitable to assess duration of action of a particular antihypertensive agent. Among these markers, those related to arterial rigidity may be of particular interest when evaluated together with ambulatory BP measurements (3,4).

Although calcium antagonists have been extremely useful in various cardiovascular disorders, the relatively short duration of action of currently available agents has required dosing three to four times a day. Nitrendipine is a long-acting dihydropyridine that reduces high BP through its peripheral vasodilating effects on vascular smooth muscle cells (5). Some investigators reported that with single daily administration nitrendipine was able to control high BP, whereas others have demonstrated a complete 24-h antihypertensive effect with only two administrations a day (6–11), but no double-blind versus placebo study has assessed the long duration of arterial and antihypertensive effects of once-daily oral administration.

The purpose of this study was two-fold: (a) to analyze the effects of once-daily oral administration of 20 mg nitrendipine on arterial distensibility, using carotid-femoral, brachial-radial, and femoral-tibial measurements of pulse wave velocity evaluated 24 h after the last drug administration; and (b) to in-

Received March 10, 1992; revision accepted June 19, 1992.
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vestigate the effects of this dihydropyridine derivative on the circardian rhythm of arterial pressure and heart rate (HR) in hypertensive subjects, using 24-h ambulatory monitoring.

MATERIAL AND METHODS

Study design

The trial consisted of two phases: a 15-day placebo-washout period and a double-blind randomized parallel group period with administration of either placebo or nitrendipine 20 mg once daily for 4 weeks. At the initial visit, patients were instructed to discontinue all antihypertensive therapy and received placebo for 15 days in single-blind fashion. At the end of this period, only patients with supine diastolic BP (DBP) (mercury sphygmomanometer as indicated below) ≥95 mm Hg were eligible for the randomized, double-blind phase. At this stage, between 8 a.m. and 10 a.m., each patient received the last placebo tablet and underwent 24-h ambulatory BP monitoring; the next day, the recorder was stopped, and mercury sphygmomanometer BP measurements and pulse wave velocity determinations were made. Patients then were randomized in a double-blind parallel group and received either placebo or nitrendipine 20 mg once daily for 4 weeks. At the end of this period, each patient received the last tablet between 8 a.m. and 10 a.m. and underwent the same investigations (BP monitoring, mercury sphygmomanometer measurements, and pulse wave velocity determination) under the same conditions and design as that of the first visit.

Patients

Twenty-two hypertensive patients were preselected for the study. Five of them were placebo-responders after the washout period. Seventeen patients (14 men and 3 women) aged 39–64 years (mean age 50 ± 8 years, ±1 SD), mean weight 76 ± 12 kg, and mean height of 171 ± cm, entered the second phase of the trial. They were randomized in two double-blind parallel groups: one group of 9 patients (7 men and 2 women: mean age 51 ± years, mean weight 76 ± 14 kg, and mean height 170 ± 10 cm) received placebo; the other group of 8 patients (7 men and 1 woman: mean age 49 ± 8 years, mean weight 77 ± 10 kg, and mean height 172 ± 6 cm) received nitrendipine (20 mg once daily) for 4 weeks).

All patients had essential, moderate, and uncomplicated hypertension. Secondary causes of hypertension were excluded on the basis of thorough clinical and biologic investigations as previously described (12). None of the 17 subjects had clinical evidence of congestive heart failure, coronary insufficiency, or other occlusive artery disease, vascular heart disease, or neurologic impairment. All patients gave their written consent to the investigation. The protocol was approved by the hospital's ethical committee.

Mercury sphygmomanometer

Arterial BP was measured after 10-min rest in the supine position and after 2 min in the standing position with the patient's arm supported at heart level. An average of three measurements was taken for each patient. Phase I Korotkoff sounds was used for determination of systolic BP (SBP), and phase V was used for evaluation of DBP. Mean BP was calculated as the sum of DBP plus one third of pulse pressure. The measurements were performed before and 24 h after the last tablet of drug intake.

Noninvasive 24-h BP monitoring

Automated BP monitoring was performed in each patient with a Novacor apparatus model Diasys 200-R-(Reuil, Malmaison, France) to measure and record BP and HR for a 24-h period. The reliability of the method was described in detail previously (13,14). Recordings were performed every 15 min during the 24-h period. Ambulatory monitoring was performed for an entire active day; the patient worked as usual during the day and then went home as usual in the evening. Each patient was required to record daily activities on a diary card. Recordings that showed an inconsistent increase or decrease in SBP or DBP without HR changes and readings with a calculated pulse pressure <10 mm Hg were deleted before data were analyzed further (15,16).

Each entire-day recording was divided into an activity (or diurnal) period (from 7 a.m. to 10 p.m.) and a nonactivity (or nocturnal) period (from 10 p.m. to 7 a.m.) based on the mean of all patients' diaries and activities. The mean values were used for statistical evaluation.

Pulse-wave velocity

For determination of pulse wave velocity, five different Doppler flow recordings were obtained at five sites: at the base of the neck for the common carotid artery, over the right brachial and radial arteries, and over the right femoral and tibial arteries. Flow was measured with a continuous Doppler unit (Sega-M842-4 or 8 MHz, U.S.A.) with handheld probes. Transcutaneous Doppler flow waves were recorded simultaneously with two ECG leads on a paper recorder at high speed (150 mm/s). Pulse wave velocity was determined as foot-to-foot velocity. The foot of the flow wave was identified as the point of the beginning at the sharp systolic upstroke. When this point could not be identified precisely, a tangent was drawn to the last part of the preceding flow wave and to the upstroke of the next wave; the foot wave was taken as the point of intersection of these two lines. Time delay was measured between the feet of the flow waves, and the ECG signal was recorded simultaneously with each of these different flow waves. The average of 10 beats was considered pulse transit time, and the mean value of two different observers' readings was taken for statistical analysis. The distance traveled by the pulse wave was measured over the body surface as the distance between the different recording sites. Arterial pulse wave was calculated as the ratio between recording sites. Arterial pulse wave was calculated as the ratio between distance and transit time. The reproducibility of the measurements was described in detail previously (12,17).

Statistical analysis

Statistical analyses were performed with SAS software (Statistical Analysis System; NC, U.S.A.) Results are mean values ± SD. Within-group comparisons were made with the sign-rank test, between-group comparisons were made with the Wilcoxon test. Ambulatory data were analyzed by analysis of variance after measurements were pooled for 2 h. Model factors were: treatment group, patient within treatment group, time and time by treatment group interaction (18). Normality and homosedasticity were checked a posteriori by graphical means.

All tests were interpreted two-sided and alpha error was fixed at 5%.

RESULTS

Sphygmomanometer measurements

Table 1 shows the sphygmomanometer measurements at baseline and their changes after treatment. Based on intergroup comparison, there was a significant decrease in SBP (-15.1 ± 9.6 mm Hg; $p = 0.002$), and DBP (-7.6 ± 5.01 mm Hg; $p = 0.01$) after nitrendipine administration. HR increased significantly ($+6.1 \pm 9.1$ beats/min; $p = 0.02$).

BP monitoring

Figures 1 and 2 show ambulatory BP and HR values in the placebo and nitrendipine groups, before and after treatment. Comparison of the mean values, calculated on the basis of all 24-h measurements, indicated that after nitrendipine administration a significant decrease in SBP (before = 147 ± 7 mm Hg; after = 139 ± 5 mm Hg; $p = 0.008$) and DBP (before = 106 ± 11, after = 100 ± 10 mm Hg; $p = 0.008$) was observed, whereas HR remained unchanged. Analyses of the ambulatory recording during the activity period (7 a.m. to 10 p.m.) and the nocturnal period (10 p.m. to 7 a.m.) are also shown in Figs. 1 and 2. No significant change was noted in the placebo group. Nitrendipine caused a significant decrease in both SBP (before = 154 ± 9, after = 144 ± 7 mm Hg; $p = 0.008$) and DBP (before 111 ± 12, after = 102 ± 9 mm Hg; $p = 0.008$) only during the day. No change was noted for the nocturnal period for either SBP (before = 134 ± 10, after = 132 ± 6 mm Hg; NS) or DBP (before = 100 ± 13, after = 96 ± 11 mm Hg; NS).

Figure 3 shows the previous results and compares the changes in ambulatory BP and HR monitoring measured every 2 h after placebo and nitrendipine administration. The values were expressed as the difference between baseline and treatment and compared statistically between the placebo and nitrendipine groups every 2 h. There was a significant difference for BP morning value but not for the nocturnal value, although a significant difference was evident after 7 a.m. ($p < 0.01$). No similar result was observed for HR.

TABLE 1. *Changes in BP and HR (sphygmomanometer measurements)*

Parameter	Placebo	Nitrendipine	p-Value (intergroup comparison)
Systolic BP (mm Hg)			
Before treatment	158 ± 7	160 ± 6	NS
After treatment	0.6 ± 4.8	−15.1 ± 9.6[a]	0.002
Diastolic BP (mm Hg)			
Before treatment	104 ± 5	103 ± 7	NS
After treatment	−1.4 ± 2.2	−7.6 ± 5.0[a]	0.01
HR (beats/min)			
Before treatment	70 ± 9	71 ± 9	NS
After treatment	−1.3 ± 3.5	+6.1 ± 9.1[c]	0.02

BP, blood pressure; HR, heart rate.
Values are ±1 SD.
[a] $p < 0.001$, [b] $p < 0.01$, and [c] $p < 0.05$ (before versus after treatment).

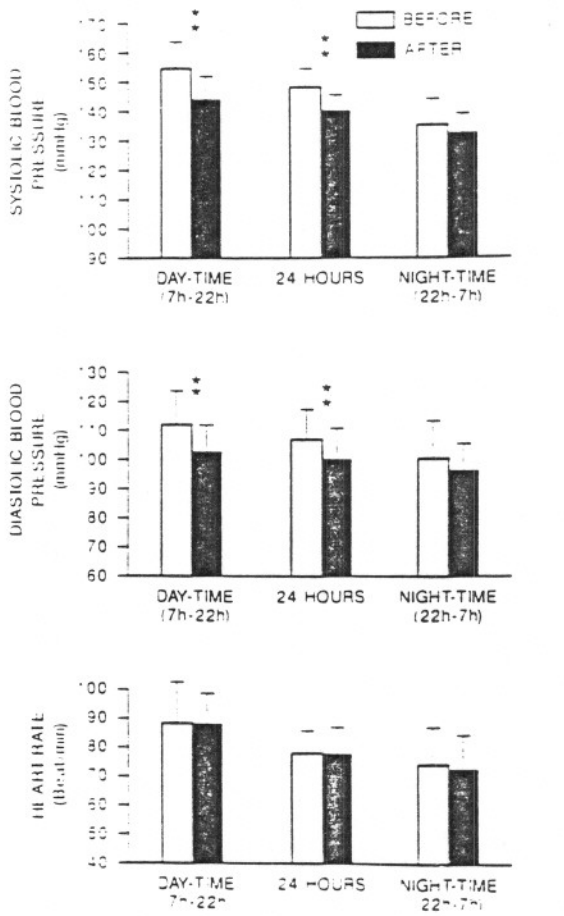

FIG. 1. Values of ambulatory blood pressure measurements before and after 1 month of treatment with nitrendipine 20 mg once daily between 8 a.m. and 10 a.m. (**$p < 0.01$).

To study the drug effect in the last 6-h period of the investigation, we analyzed the last three 2-h periods separately. Ambulatory data were pooled as follows: from 4 a.m. to 6 a.m., from 6 a.m. to 8 a.m., and from 8 a.m. to 10 a.m. Figure 4 shows the changes in SBP and DBP observed in the placebo and nitrendipine groups. Based on intergroup comparison, BP increased slightly after placebo and decreased significantly after nitrendipine administration.

Arterial distensibility

Table 2 shows the mean values of pulse wave velocity and their changes after treatment. No significant modification was observed in the placebo group. In the nitrendipine group, carotid-femoral pulse wave velocity decreased significantly (-1.0 ± 1.2 m/s; $p < 0.05$-intragroup comparison) (Fig. 5). No significant correlation was observed between the changes in BP and the changes in pulse wave

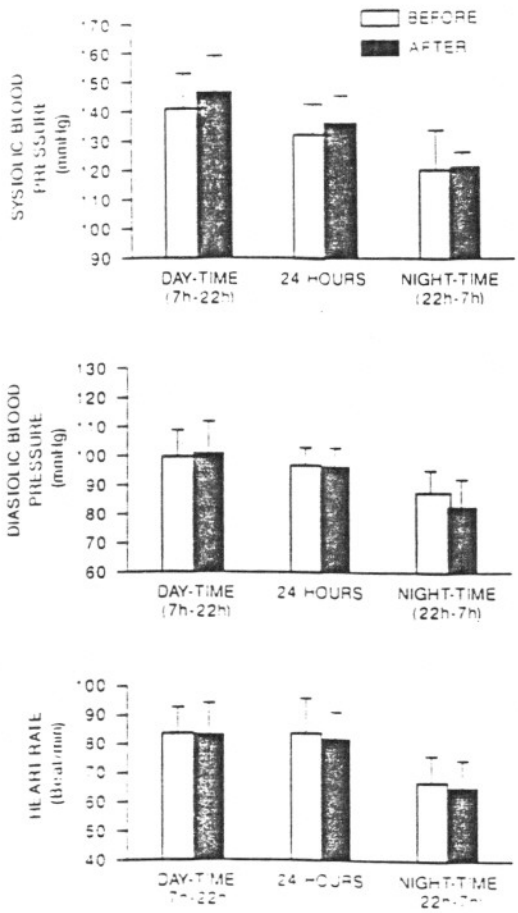

FIG. 2. Values of ambulatory blood pressure measurements before and after 1 month of placebo treatment.

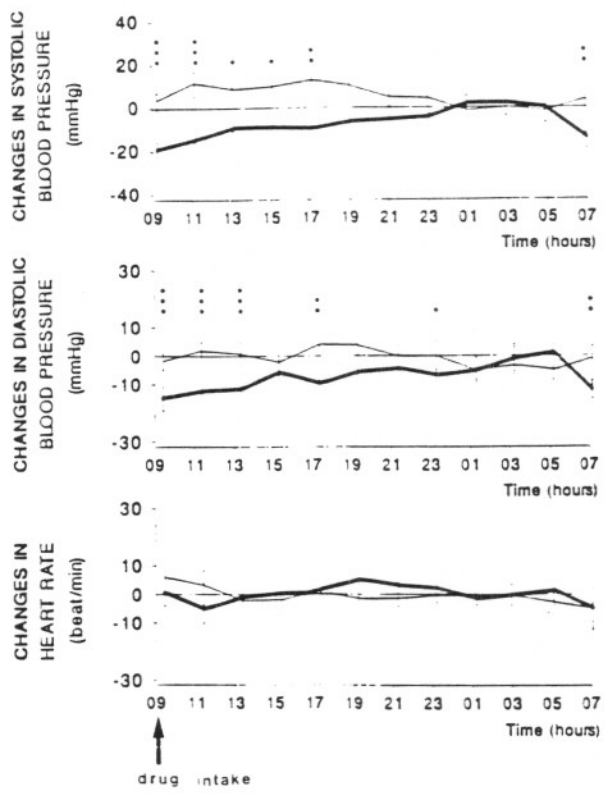

FIG. 3. Ambulatory blood pressure changes before and 1 month after nitrendipine (20 mg) or placebo administered once daily between 8 a.m. and 10 a.m.: statistical comparison (*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$). Placebo (thin line), nitrendipine (thick line).

velocity. Based on intergroup comparison, brachial-radial pulse wave velocity decreased after nitrendipine (nitrendipine = -0.8 ± 1.5; placebo = -0.4 ± 0.6 m/s; $p = 0.04$). Femoral-tibial pulse wave velocity did not change.

DISCUSSION

In recent years, several methods of analyzing ambulatory BP monitoring data, have been evaluated particularly methods for determining the effect of antihypertensive drug therapy. The most commonly used methods include calculation of mean or median values during awake and sleep periods, assessment of BP variability and distribution, calculation of BP load, and integration of the area under the BP curve over time (1,2). However, examination of the circadian rhythm in a 24-h BP profile is the most helpful aid in assessing duration of the antihypertensive effect of a drug under investigation. In the present study, although a clear and significant decrease in BP was observed during the day, no substantial change was observed during the most important part of the night, suggesting that nitrendipine did not act all day on the vessels. We believe, however, that this latter finding should be interpreted very cautiously for several reasons. First because BP is physiologically lower during the night than during the day, it is often difficult to demonstrate a significant nocturnal BP reduction. Indeed, according to the law of initial value (19), the decrease in BP is expected to be modest when baseline BP is low, as observed nocturnally. Second, in our investigation, sphygmomanometer BP measurements showed a significant reduction 24 h after last administration of the drug. Third, the early morning increase in BP was diminished after nitrendipine administration (Figs. 3 and 4).

The physiologic nocturnal decrease in BP is as-

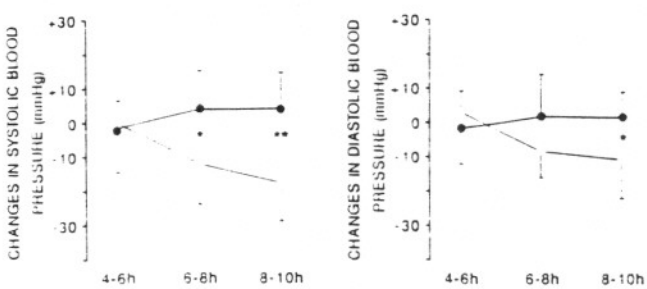

FIG. 4. Changes in blood pressure monitoring during the late period (4 a.m. to 10 a.m.) and after last tablet intake between 8 a.m. and 10 a.m. once daily for 1 month. Comparison between placebo (solid circles) and nitrendipine 20 mg (open circles) (*$p < 0.05$, **$p < 0.01$).

TABLE 2. *Changes in pulse wave velocity*

Pulse wave velocity (m/s)	Placebo	Nitrendipine	p-Value (intergroup comparison)
Carotid femoral			
Before treatment	9.8 ± 1.6	10.7 ± 2.5	NS
After treatment	0.0 ± 0.8	−1.0 ± 1.2[a]	NS
Femoral-tibial			
Before treatment	12.9 ± 1.3	13.2 ± 2.2	NS
After treatment	−0.1 ± 1.0	−0.7 ± 2.0	NS
Brachial-radial			
Before treatment	12.2 ± 1.4	12.7 ± 2.5	NS
After treatment	−0.4 ± 0.6	−0.8 ± 1.5	0.04

Values are ±1 SD.
[a] $p < 0.05$ (before vs. after treatment).

sociated with a decrease in the activity of the autonomic nervous system. On the basis of plasma catecholamine determinations and spectral analysis of HR and BP, studies in humans have shown a reduction in the markers of sympathetic activity and an increase in those of vagal activity (20,21). In addition, the bradycardic response to baroreceptor stimulation increases during the night (22,23). All these mechanisms are reversed just before awakening, in association with the rapid increase in BP observed in the early morning (24). In the present study, this early morning BP increase was diminished by nitrendipine, as previously observed after administration of drugs related to α-adrenoceptors such as labetolol (25–27). Thus, nitrendipine may have specifically antagonized the increase in activity of the autonomic nervous system during the early morning through peripheral or even central pathways (28,29). Whatever the mechanism(s) may be, this finding supports the possibility of long-term duration of the antihypertensive effect of nitrendipine administration once daily.

Taking into account that the analysis of the BP changes provides only weak evidence for long-term effect of nitrendipine, one of our principal findings

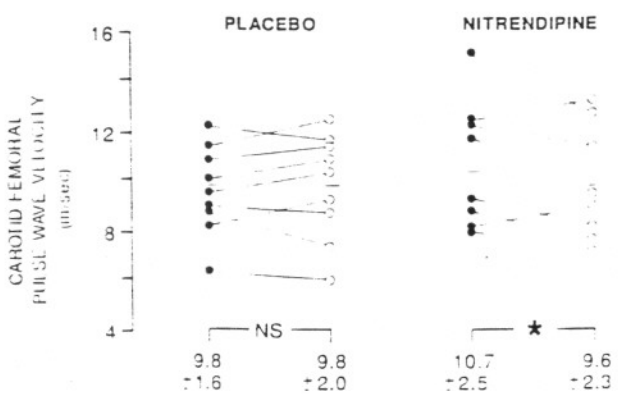

FIG. 5. Carotid-femoral pulse wave velocity values measured before and at 24 h after last tablet intake of placebo or nitrendipine 20 mg once daily for 1 month (*$p < 0.05$). Before (solid circles) and after (open circles) administration.

was the decrease in carotid-femoral and brachial-radial pulse-wave velocities observed after nitrendipine administration. This result indicates an improvement in arterial distensibility, which is known to be reduced in subjects with untreated hypertension (12). A similar result was observed with nitrendipine in hypertensive hemodialyzed subjects with end-stage renal failure (30). In these particular subjects, however, arterial improvement required several weeks of treatment, probably owing to the important structural changes in the large arteries. Arterial improvement has been also observed in acute situations using nifedipine and nicardipine in mild-to-moderate hypertension (4). In the present study, the increase in arterial distensibility occurred 24 h after the last administration of the drug. The decrease in carotid-femoral pulse-wave velocity might be the simple consequence of the BP reduction since the aorta is a predominantly elastic artery and therefore very sensitive to pressure changes. In this investigation, however, no significant correlation was observed between the change in carotid-femoral pulse-wave velocity and the change in BP. Furthermore, a significant decrease in pulse wave velocity (Table 2) was observed at the site of the brachial artery, and no change was observed at the site of the brachial artery, and no change was observed at the site of the femoral-tibial arteries for the same mean BP reduction. These findings indicate that the changes in pulse wave velocity were not the simple consequence of BP reduction and predominated in muscular arteries (such as the brachial artery) even 24 h after the last administration of nitrendipine.

We showed that a single dose of 20 mg nitrendipine administered once daily effectively improves arterial distensibility in hypertensive subjects for 24 h, in association with a decrease in BP. Interactions with the autonomic nervous system occur during early morning, with a decrease in BP.

Acknowledgment: This study was supported by a grant from the Institut National de la Santé et de la Recherche Médicale (INSERM U. 337) and the Ministère de la Recherche, Paris, France. We thank Dr. Berdeaux for statistical analysis, and Jacqueline Dore for excellent secretarial assistance.

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